IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION OF	)
	) ART UNIT: 1644
Arnold I. Levinson *et al.*	)
	) Michael Edward Szperka
APPLICATION NUMBER: 10/518,701	)
	)
FILED: September 1, 2005	)
	)

TITLE: VACCINES FOR SUPPRESSING IGE-MEDIATED ALLERGIC DISEASE AND METHODS FOR USING THE SAME

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal was commenced by a Notice of Appeal filed and a Request for Pre-Appeal Conference Review on July 23, 2009. A decision was mailed on September 1, 2009 in response to the request for Pre-Appeal Conference Review. This Appeal Brief is timely filed in view of the petition for extension of time enclosed herewith, which extends the time to file the present Appeal Brief to and through March 1, 2010. The Notice of Appeal appeals the final rejection of claims 1-3, 5-8, 22-24, 26-29 and 32-37, and 50-73.

The headings used hereinafter and the subject matter set forth under each heading is in accordance with 37 C.F.R. §41.37(c).

I. REAL PARTY IN INTEREST

Arnold I Levinson, Sandra Calarota, David B. Weiner, Miguel Otero are the only inventors of the invention described and claimed in the above-identified application. Sandra Calarota, David B. Weiner, Miguel Otero have assigned all rights, title, and interest in the invention of the application to The Trustees of the University Of Pennsylvania as evidenced by assignment which was filed with the United States Patent and Trademark Office (USPTO) and recorded on reel 021369, frame 0519; reel 021550, frame 0980; reel 021974, frame 0052. Additionally, Inovio BioMedical Corporation is the exclusive licensee of the above-identified application. Accordingly, Inovio BioMedical Corporation is the Appellant and the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellant, the Appellant's legal representative or the inventors, which will directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

III. STATUS OF CLAIMS

The present application was filed with Claims 1-31.

Claims 32-73 have been added during prosecution

Claims 4, 9-21, 25, 30, 31, and 38-49 have been canceled.

Claims 1-3, 5-8, 22-24, 26-29 and 32-37, and 50-73 remain pending in the present application and are currently rejected.

The claims on Appeal are pending claims 1-3, 5-8, 22-24, 26-29 and 32-37, and 50-73.

Particularly, Claims 1-3, 5-7, 22-24, stand 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent 4,769,326).

Claims 1-3, 5-7, 22-24, and 26-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Claims 1-3, 5-7, 22-24, and 26-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Claims 8, 32-37, 50, and 58-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of. Rutter (US Patent 4,769,326) and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 58-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. WO 02/20038 in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 58-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids

Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 66-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 66-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

IV. STATUS OF AMENDMENTS

The Amendment filed on May 27, 2008 in response to the Restriction Requirement dated November 26, 2007 was entered. The Amendment filed on November 13, 2008 in response to the Non-Final Office Action dated August 13, 2008 was entered. The Amendment filed March 23, 2009 in response to the Final Office Action dated January 23, 2009 was entered.

The claims on appeal are pending claims 1-3, 5-8, 22-24, 26-29 and 32-37, and 50-73 as included in the Claims Appendix herein.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claims of the present application are directed to isolated nucleic acid molecules, vaccines, host cells, methods of producing a protein comprising an IgE leader sequence and various embodiments thereof.

Claim 1

Independent claim 1 is directed to an isolated nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one nonIgE helper T cell epitope, and being free of epitopes of serum IgE, wherein the epitope of membrane IgE and the nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence.

Independent claim 1 is described in detail in the specification, for example, on page 2, line 23 through line 30; and page 5, lines 20-30 and throughout the application.

Claim 8

Independent claim 8 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent.

Independent claim 8 is described in detail in the specification, for example, on page 2, lines 24-32 and throughout the application.

Claim 22

Independent claim 22 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one nonIgE helper T cell epitope, and being free of epitopes of serum IgE, wherein said epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence.

Independent claim 22 is described in detail in the specification on page 2, line 23 through line 30; page 5, lines 20-30, page 16, lines 13-21 and originally filed claim 22, among other locations.

Claim 28

Dependent claim 28, which depends upon the host cell of claim 22, is directed to a method of producing a protein comprising at least one membrane IgE and at least one non-IGE helper T cell epitope and being free of epitopes of serum IgE, wherein said epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence comprising culturing a host cell of claim 22 and isolating said protein expressed thereby.

Dependent claim 28 is described in detail in the specification on page 2, line 23 through line 30; page 5, lines 20-30, page 16, lines 13-21, among other locations.

Claim 34

Dependent claim 34, which depends upon the vaccine composition of claim 8 further comprising coding sequence encoding at least one non-IgE helper T cell epitope.

Dependent claim 34 is described in detail in the specification at, for example, on page 2, lines 24-32 and throughout the application.

Claim 50

Dependent Claim 50, which depends upon claim 1, is directed to a An isolated nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one nonIgE helper T cell epitope, and being free of epitopes of serum IgE, wherein said epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence, further comprising coding sequence encoding an IgE leader sequence.

Dependent claim 50 is described in detail in the specification on page 2, line 23 through line 30, and page 5, lines 20-30, and throughout the application.

Claim 51

Independent claim 51 is directed to an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE.

Independent claim 51 is described in detail in the specification on page 2, line 23 through line 30, among other locations.

Claim 58

Dependent claim 58, which depends upon the vaccine composition of claim 34, wherein the at least one epitope of membrane IgE and said at least one non-IgE helper T cell epitope are fused by a proteolytic cleavage sequence.

Dependent claim 58 is described in detail in the specification on page 2 page 2, lines 24-32 and page 5, lines 20-30, and throughout the application.

Claim 59

Independent claim 59 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one non-IgE helper T cell epitope, being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent, wherein said at least one epitope of membrane IgE and said at least one non-IgE helper T cell epitope are fused by a proteolytic cleavage sequence.

Independent claim 59 is described in detail in the specification on page 2, line 23 through line 32; and page 5, lines 20-30, page 6, lines 9-14 among other locations.

Claim 65

Dependent claim 65, which depends upon the host cell of claim 22, is directed to a host cell of claim 22 wherein the nucleic acid molecule further comprises a coding sequence encoding an IgE leader sequence.

Claim 66

Independent claim 66 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE.

Independent claim 66 is described in detail in the specification on page 2, line 23 through line 30; page 5, lines 20-30, page 16, lines 13-21 and originally filed claim 22, among other locations.

Claim 72

Dependent claim 72, which depends upon the host cell of claim 66 is directed to a method of producing a protein comprising an IgE leader sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell of claim 66 and isolating said protein expressed thereby.

Dependent claim 72 is described in detail in the specification on page 2, line 23 through line 30; page 5, lines 20-30, page 16, lines 13-21, among other locations.

VI. GROUND OF REJECTIONS TO BE REVIEWED ON APPEAL

Whether claims 1-3, 5-7, 22-24, and 26-29 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent 4,769,326).

Whether claims 1-3, 5-7, 22-24, and 26-29 should be rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Whether claims 1-3, 5-7, 22-24, and 26-29 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Whether claims 8, 32-37, 50, and 58-73 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of. Rutter (US Patent 4,769,326) and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Whether claims 8, 32-37, 50, and 58-73 should be rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 9/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Whether claims 8, 32-37, 50, and 58-73 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

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VII. ARGUMENTS

The Arguments made in the Pre-Appeal Conference Request dated July 23, 2009; the Response dated March 23, 2009 in response to the Final Office Action dated January 23, 2009; the Response dated November 13, 2008 in response to the Non-Final Office Action dated August 13, 2008 are hereby fully incorporated by reference. Each ground of rejection presented for review is addressed hereinafter under the appropriate heading.

For the reasons discussed in more detail below, each of the claims presented in the pending application are not rendered obvious and, as a result, the final rejections presented in the January 23, 2009 Office Action are improper.

A. Claims 1-3, 5-7, 22-24, and 26-29 are Not Obvious in view of Chen *et al.* (WO 98/53843) in view of Wang *et al.* (WO 99/67293) in view of Hollis *et al.* (U.S. Patent No. 5,629,415) and in view of Rutter (U.S. Patent No. 4,769,326).

Claims 1-3, 5-7, 22-24, and 26-29 are not obvious in view of the cited references because the combination of the references teaches away from the presently claimed invention. Claim 1 is directed to a nucleic acid molecule. The nucleic acid molecule encodes a protein comprising at least one epitope of membrane IgE and at least one nonIgE helper T cell epitope, and being free of epitopes of serum IgE. Additionally, claim 1 recites that the epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence. Not only do Chen and Wang fail to teach or suggest a proteolytic cleavage sequence, but Chen and Wang teach away from using a proteolytic cleavage sequence. Accordingly, the combination of the references fails to render claims 1-3, 5-7, 22-24, and 26-29 obvious.

To determine obviousness, a four part test, as set forth in Graham v. John Deere Co., is employed to examine the: (i) content and scope of the prior art; (ii) level of ordinary skill in the art; (iii) differences between the prior art and the claimed invention; and (iv) objective evidence of non-obviousness.[1] To establish a *prima facie* case of obviousness, the references must yield the presently claimed invention, the references cannot teach away from the presently

[1] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1320 (Fed. Cir. 2004).

claimed invention and there must be some reasoning to combine the references. [2] The reason need not be a precise teaching directed to the specific subject matter of the claim. *KSR v. Teleflex*, S. Ct. 2007.

The Office alleges that the Chen reference discloses nucleotide vaccine constructs comprising the membrane bound domain of IgE coupled to heterologous sequences including helper T epitopes. The Office acknowledges that the Chen reference fails to disclose a fusion protein with a proteolytic cleavage sequence. The Office alleges the deficiency is remedied by the Rutter reference which allegedly discloses the use of linkers comprising proteolytic cleavage sites because the linkers "allow for efficient incorporation and removal of desired functional properties." (Final Office Action, dated January 23, 2005 p. 5). The Office alleges that Wang discloses disclose vaccine constructs wherein IgE sequence is coupled to T-helper epitopes such as those from tetanus toxoid, wherein the administered construct is a nucleic acid. Hollis allegedly discusses recombinant IgE encoding polynucleotides can be inserted in to plasmid vectors and used to generate a wide variety of host cells including bacterial and mammalian cells. The Office's conclusion that claims 1-3, 5-7, 22-24, and 26-29 are obvious is improper. The rejection is improper because the obviousness rejection is not supported by the totality of the references when the Chen and Wang references are read in their entirety as they would be by one of skill in the art.

Claims 1-3, 5-7, 22-24, and 26-29 are not obvious because the Office has failed present a proper *prima facie* obviousness rejection because the cited references teach away from the claimed invention. A "reference teaches away if it leaves the impression that the product would not have the property sought by the applicant." *In re Gurley*, 27 F. 3d 551, 553 (Fed. Cir. 1994, citing *In re Caldwell*, 319 F.2d 254, 256 (C.C.P.A. 1963)). Here, the Chen and Wang references teach that the product should not contain a proteolytic cleavage sequence.

The Chen and Wang references teach away from using a proteolytic cleavage sequence. The presence of the cleavage sequence in the presently claimed invention allows the components of the fusion protein to be separated into 2 components once the cleavage sequence is cleaved. One of skill in the art reading the Chen and Wang references would be led to use a composition that conjugates the two components without the two components being able to be

[2] MPEP §2143.

cleaved. For example, the Chen reference repeatedly describes conjugates and does not state that the conjugated composition can include a cleavage sequence. Additionally, the Chen reference states that for conjugates in human use one would expect that there would be "no inhibition of IgE responses to ***unrelated***, ***unconjugated*** antigens." (Chen, p. 10, line 22, emphasis added.).

> 'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'

Optivus Tech., Inc. v. Ion Beam Applications S.A., 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)). Here, the Chen reference teaches away because it states that there would be no inhibition of IgE responses for unrelated, unconjugated antigens. In the presently claimed invention, the antigens would become unrelated and unconjugated once the proteolytic cleavage sequence is cleaved. When introduced into physiological conditions the cleavage sequence would be cleaved by a protease and lead to unrelated, unconjugated antigens, which Chen teaches will lead to an undesirable result. Therefore, one of skill in the art reading the Chen reference in its entirety would not have inserted a proteolytic cleavage sequence because such a construct would lead to an unconjugated composition leading to a result that is explicitly not desired by the Chen reference. One of skill in the art reading Chen in its entirety would be discouraged from including a cleavage sequence because this would lead to a result that is the opposite of what Chen teaches, that is that the antigens need to be conjugated. Accordingly, the Chen reference teaches away from using a construct that would allow the epitopes to be separated by use of a cleavage sequence.

The Wang reference also teaches away from including a proteolytic cleavage sequence. The Wang reference discloses the use of a spacer between its components and states that the two components are "adjacent to either the N- or C-terminus of IgE-CH3 domain antigen sequences, ***in order to evoke efficient*** antibody responses." (Wang, p. 28-29). Like the Chen reference, the Wang reference teaches that the components should be next to one another and linked so that there is a proper response. Wang expressly states that in order to evoke an efficient antibody response the components are adjacent. Therefore, Wang teaches away from the presently claimed invention because it states that the epitopes must be next to one another. In contrast, claim 1 recites that the epitopes are separated by a cleavage sequence. The presence of an epitope sequence would separate the epitopes enough that they would not be considered adjacent

to one another. Additionally, once the cleavage sequence is cleaved the epitopes would no longer be physically connected through any linker let alone be considered adjacent to one another. Additionally, the Wang reference fails to suggest decoupling the components and teaches away from such a method because decoupling would not "evoke [an] efficient antibody response[]." (*Id.*)

The Advisory Action dated April 7, 2009 argues that the proteolytic cleavage sequence may not be cleaved *in vivo* and that separation is not a limitation of the claim. The Office's assertion is reading the limitation out of the claim. The cleavage sequence is a functional cleavage sequence otherwise the term cleavage sequence would have no meaning. One of skill in the art reading the presently claimed invention as described in claims 1-3, 5-7, 22-24, and 26-29 would understand that the purpose of the cleavage sequence is to allow the epitopes to be separated and not to keep them adjacent to one another as Chen and Wang teaches. Therefore, one of skill in the art reading the cited references would not have added a cleavage sequence because the purpose of including a cleavage sequence is to allow the parts to be separated, which is exactly what the references teach away from.

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Wang and Chen references teach away from allowing the components to be separated. In view of the foregoing, Applicants respectfully request that the rejection of claims 1-3, 5-7, 22-24, and 26-29 under 35 U.S.C. § 103(a) be withdrawn.

B. Claims 1-3, 5-7, 22-24, and 26-29 are Not Obvious In View of Klysner *et al.* (WO 02/20038) in view of Wang *et al.* (WO 99/67293) and in view of Rutter (U.S. Patent No. 4,769,326).

Claims 1-3, 5-7, 22-24, and 26-29 are not obvious because Klysner and Wang teach away from the presently claimed invention. Claim 1 recites that the epitope of membrane IgE and the nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence. Not only do Klysner and Wang fail to teach or suggest a proteolytic cleavage sequence, but Klysner and Wang teach away from using a proteolytic cleavage sequence. Accordingly, the combination of the references fails to render claims 1-3, 5-7, 22-24, and 26-29 obvious. The Office acknowledges that the Klysner and Wang references fail to disclose the use of linkers comprising

a proteolytic cleavage sequence between the epitopes. (Final Office Action, page 6). The Office alleges that the Rutter reference cures this deficiency. The Rutter reference, however, cannot cure this deficiency because Klysner and Wang teach away from including a proteolytic cleavage sequence.

The claims are not obvious because the Klysner and Wang references each teach away from inserting a proteolytic cleavage sequence. The Wang reference teaches away for the reasons stated above and are hereby incorporated by reference.

Klysner also teaches away from the presently claimed invention because Klysner teaches that the epitopes should be simultaneously presented to the antigen presenting cells. (Klysner, entire document and, p. 13, lines 14-20). The inclusion of a proteolytic cleavage sequence that allows the epitopes to be separated would function to eliminate the likelihood of simultaneous presentation of the epitopes by the antigen presenting cells. "'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'" *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)). One of skill in the art would not have been led to insert a proteolytic cleavage sequence because it would be contrary to what the Klysner reference states is necessary for an effective use. Klysner teaches the simultaneous presentation of the epitopes by the antigen presenting cells. That is one of skill in the art would be discouraged from following the path of including a proteolytic cleavage sequence because both Klysner and Wang teach that keeping the epitopes together is important for the desired outcome. Thus, both the Klysner and Wang references teaches away from using a proteolytic cleavage sequence. The Office's use of Rutter to include a proteolytic cleavage sequence is improper because it contradicts the teachings of Klysner and Wang.

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Klysner and Wang references teach away from allowing the components to be separated and, therefore, a cleavage sequence based upon Rutter would not have been included. In view of the foregoing, Applicants respectfully request that the rejection of claims 1-3, 5-7, 22-24, and 26-29 under 35 U.S.C. § 103(a) be withdrawn.

C. Claims 1-3, 5-7, 22-24, and 26-29 are Not Obvious In View of Klysner *et al.* (US 2002/0172673)[3] in view of Wang *et al.* (WO 99/67293) and in view of Rutter (U.S. Patent No. 4,769,326).

Claims 1-3, 5-7, 22-24, and 26-29 are not obvious because Klysner and Wang teach away from the presently claimed invention. Claim 1 recites that the epitope of membrane IgE and the nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence. Not only do Klysner and Wang fail to teach or suggest a proteolytic cleavage sequence, but Klysner and Wang teach away from using a proteolytic cleavage sequence. Accordingly, the combination of the references fails to render claims 1-3, 5-7, 22-24, and 26-29 obvious. The Office acknowledges that the Klysner and Wang references fail to disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes. (Final Office Action, page 6). The Office alleges that the Rutter reference cures this deficiency. The Rutter reference, however, cannot cure this deficiency because Klysner and Wang teach away from including a proteolytic cleavage sequence.

The claims are not obvious because the Klysner and Wang references each teach away from inserting a proteolytic cleavage sequence. The Wang reference teaches away for the reasons stated above and are hereby incorporated by reference.

Klysner also teaches away from the presently claimed invention because Klysner teaches that the epitopes should be simultaneously presented to the antigen presenting cells. (Klysner, entire document and, p. 13, lines 14-20). The inclusion of a proteolytic cleavage sequence that allows the epitopes to be separated would function to eliminate the likelihood of simultaneous presentation of the epitopes by the antigen presenting cells. "'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'" *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)). One of skill in the art would not have been led to insert a proteolytic cleavage sequence because it would be contrary to what the Klysner reference states is necessary for an

[3] Applicants note that Klysner (US 2002/0172673) and Klysner (WO 02/20038) references are the same. Page and line number refer to WO 02/20038.

effective use. Klysner teaches the simultaneous presentation of the epitopes by the antigen presenting cells. That is one of skill in the art would be discouraged from following the path of including a proteolytic cleavage sequence because both Klysner and Wang teach that keeping the epitopes together is important for the desired outcome. Thus, both the Klysner and Wang references teaches away from using a proteolytic cleavage sequence. The Office's use of Rutter to include a proteolytic cleavage sequence is improper because it contradicts the teachings of Klysner and Wang.

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Klysner and Wang references teach away from allowing the components to be separated and, therefore, a cleavage sequence based upon Rutter would not have been included. In view of the foregoing, Applicants respectfully request that the rejection of claims 1-3, 5-7, 22-24, and 26-29 under 35 U.S.C. § 103(a) be withdrawn.

D. Claims 8, 32-37, 50, and 58-73 are Not obvious over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of. Rutter (US Patent 4,769,326) and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the references fails to teach all the elements of the claim. Claim 8 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent. Claim 50 is directed to a nucleic acid molecule comprising, in part, an IgE leader sequence. Claim 66 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE. Claim 72 is directed to a method of producing a protein comprising an IgE leader sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell and isolating said protein expressed thereby.

The Office has failed to put forward a proper *prima facie* obviousness rejection because even when all the references are combined the combination fails to yield the presently claimed

invention. Specifically, the Office has failed to show that the combination yields a nucleic acid sequence with an IgE leader sequence or a nucleic acid sequence that encodes a protein comprising an IgE leader sequence. To determine obviousness, a four part test, as set forth in Graham v. John Deere Co., is employed to examine the: (i) content and scope of the prior art; (ii) level of ordinary skill in the art; (iii) differences between the prior art and the claimed invention; and (iv) objective evidence of non-obviousness.[4] To establish a *prima facie* case of obviousness, the references must yield the presently claimed invention, the references cannot teach away from the presently claimed invention and there must be some reasoning to combine the references.

The Office alleges that the combination of references discloses each and every element of claims 8, 32-37, 50, 58-73. In support of this contention the Office states:

> Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain . . . and thus an "IgE leader" is the ***same sequence*** as an IgM, IgD, IgG, and IgA leader sequence…Thus, the "Ig leader" of Walls *et al.* is an "IgE leader."

(Final Office Action dated January 23, 2009, pages 9-10, emphasis added). Applicants have previously submitted a declaration pursuant to 37 C.F.R. § 1.132 by Dr. David B. Weiner with the response filed March 23, 2009, which was entered into the Record by the Examiner on April 7, 2009 (copy appended hereto in Exhibits Appendix). The declaration lists the amino acid sequences from various leaders sequences and are labeled as IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1. These leader sequences have been identified by Dr. Weiner and show that not all leader sequences are the same. The declaration also shows the sequence similarity between the different leader sequences. The IgE leader sequence is not 100% identical to the other leader sequences. The declaration states, "[t]he alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes." (Weiner Declaration, ¶ 3). Therefore, the Office has

[4] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1320 (Fed. Cir. 2004).

failed to demonstrate that the "Ig leader" of the Walls reference is an "IgE leader." Therefore, the Office has failed to present a proper *prima facie* obviousness rejection because even if all the references were combined the combination does not yield the present invention. Thus, the claims are not obvious.

The Office has rejected the Declaration because of the apparent lack of Genbank Accession numbers or other source identifiers. The Office's request for Genbank accession numbers is improper. The Office cannot summarily dismiss the declaration without a reasonable basis to support its conclusion (See, *In Re Alton*, 76 F. 3d 1168, 1174-75 Fed. Cir. 1996). There is no requirement that the facts presented in the declaration be from a public database such as Genbank. The Declaration must be treated as a fact and when treated as such Applicants have provided evidence showing that not all leader sequences are the same. The Office has not provided any evidence to show that the facts presented in the declaration are incorrect. Rather than consider the evidence presented by Applicants in the declaration the Office has done what is prohibited. *Id.* When the evidence is properly considered the sequences demonstrate that not all leader sequences are the same. Therefore, the combination of the references fails to yield a composition comprising an IgE leader sequence as is presently claimed.

Accordingly, claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 8, 32-37, 50, and 58-73 be withdrawn.

E. Claims 50, 58, 59-65 Are Not Obvious over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of. Rutter (US Patent 4,769,326) and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 50 and 58-65 are also not obvious because the combination of the references teaches away from the presently claimed invention. Claims 50 and 58-65 recite in one form or another that the epitope of membrane IgE and the non-IgE helper T cell epitope are fused by a proteolytic cleavage sequence. As discussed above, Wang and Chen teach away from an epitope of membrane IgE and a non-IgE helper T cell epitope being fused by a proteolytic cleavage sequence. A "reference teaches away if it leaves the impression that the product would not have the property sought by the applicant." In re Gurley, 27 F. 3d 551, 553 (Fed. Cir. 1994, citing In

re Caldwell, 319 F.2d 254, 256 (C.C.P.A. 1963)). Here, the Chen and Wang references teach that the product should not contain a proteolytic cleavage sequence.

The rejection is improper because the obviousness rejection is not supported by the totality of the references when the Chen and Wang references are read in their entirety as they would be by one of skill in the art.

Claims 1-3, 5-7, 22-24, and 26-29 are not obvious because the Office has failed present a proper *prima facie* obviousness rejection because the cited references teach away from the claimed invention. A "reference teaches away if it leaves the impression that the product would not have the property sought by the applicant." *In re Gurley*, 27 F. 3d 551, 553 (Fed. Cir. 1994, citing *In re Caldwell*, 319 F.2d 254, 256 (C.C.P.A. 1963)). Here, the Chen and Wang references teach that the product should not contain a proteolytic cleavage sequence.

The Chen and Wang references teach away from using a proteolytic cleavage sequence. The presence of the cleavage sequence in the presently claimed invention allows the components of the fusion protein to be separated into 2 components once the cleavage sequence is cleaved. One of skill in the art reading the Chen and Wang references would be led to use a composition that conjugates the two components without the two components being able to be cleaved. For example, the Chen reference repeatedly describes conjugates and does not state that the conjugated composition can include a cleavage sequence. Additionally, the Chen reference states that for conjugates in human use one would expect that there would be "no inhibition of IgE responses to ***unrelated***, ***unconjugated*** antigens." (Chen, p. 10, line 22, emphasis added.).

> 'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'

Optivus Tech., Inc. v. Ion Beam Applications S.A., 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)). Here, the Chen reference teaches away because it states that there would be no inhibition of IgE responses for unrelated, unconjugated antigens. In the presently claimed invention, the antigens would become unrelated and unconjugated once the proteolytic cleavage sequence is cleaved. When introduced into physiological conditions the cleavage sequence would be cleaved by a protease and lead to unrelated, unconjugated antigens, which Chen teaches will lead to an undesirable result. Therefore, one of skill in the art reading the Chen reference in its entirety would not have inserted a proteolytic cleavage sequence

because such a construct would lead to an unconjugated composition leading to a result that is explicitly not desired by the Chen reference. One of skill in the art reading Chen in its entirety would be discouraged from including a cleavage sequence because this would lead to a result that is the opposite of what Chen teaches, that is that the antigens need to be conjugated. Accordingly, the Chen reference teaches away from using a construct that would allow the epitopes to be separated by use of a cleavage sequence.

The Wang reference also teaches away from including a proteolytic cleavage sequence. The Wang reference discloses the use of a spacer between its components and states that the two components are "adjacent to either the N- or C-terminus of IgE-CH3 domain antigen sequences, ***in order to evoke efficient*** antibody responses." (Wang, p. 28-29). Like the Chen reference, the Wang reference teaches that the components should be next to one another and linked so that there is a proper response. Wang expressly states that in order to evoke an efficient antibody response the components are adjacent. Therefore, Wang teaches away from the presently claimed invention because it states that the epitopes must be next to one another. In contrast, claim 1 recites that the epitopes are separated by a cleavage sequence. The presence of an epitope sequence would separate the epitopes enough that they would not be considered adjacent to one another. Additionally, once the cleavage sequence is cleaved the epitopes would no longer be physically connected through any linker let alone be considered adjacent to one another. Additionally, the Wang reference fails to suggest decoupling the components and teaches away from such a method because decoupling would not "evoke [an] efficient antibody response[]." (*Id.*)

The Advisory Action dated April 7, 2009 argues that the proteolytic cleavage sequence may not be cleaved *in vivo* and that separation is not a limitation of the claim. The Office's assertion is reading the limitation out of the claim. The cleavage sequence is a functional cleavage sequence otherwise the term cleavage sequence would have no meaning. One of skill in the art reading the presently claimed invention as described in claims 1-3, 5-7, 22-24, and 26-29 would understand that the purpose of the cleavage sequence is to allow the epitopes to be separated and not to keep them adjacent to one another as Chen and Wang teaches. Therefore, one of skill in the art reading the cited references would not have added a cleavage sequence because the purpose of including a cleavage sequence is to allow the parts to be separated, which is exactly what the references teach away from.

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Wang and Chen references teach away from allowing the components to be separated.

Accordingly, claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the cited references fails to yield the presently claimed invention, as discussed above, and the references teach away from the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 8, 32-37, 50, and 58-73 be withdrawn.

F. Claims 8, 32-37, 50, and 58-73 are Not Obvious in view of Klysner et al. (WO 02/20038) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the references fails to teach all the elements of the claim. Claim 8 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent. Claim 50 is directed to a nucleic acid molecule comprising, in part, an IgE leader sequence. Claim 66 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE. Claim 72 is directed to a method of producing a protein comprising an IgE leader sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell and isolating said protein expressed thereby.

The Office has failed to put forward a proper *prima facie* obviousness rejection because even when all the references are combined the combination fails to yield the presently claimed invention. Specifically, the Office has failed to show that the combination yields a nucleic acid sequence with an IgE leader sequence or a nucleic acid sequence that encodes a protein comprising an IgE leader sequence. To determine obviousness, a four part test, as set forth in Graham v. John Deere Co., is employed to examine the: (i) content and scope of the prior art; (ii) level of ordinary skill in the art; (iii) differences between the prior art and the claimed

invention; and (iv) objective evidence of non-obviousness.[5] To establish a *prima facie* case of obviousness, there must be some reason to combine the references and the prior art references, when combined, must teach or suggest all of the claim limitations.[6]

The Office alleges that the combination of references discloses each and every element of claims 8, 32-37, 50, 58-73. In support of this contention the Office states:

> Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain . . . and thus an "IgE leader" is the ***same sequence*** as an IgM, IgD, IgG, and IgA leader sequence…Thus, the "Ig leader" of Walls *et al.* is an "IgE leader."

(Final Office Action dated January 23, 2009, pages 9-10, emphasis added). Applicants have previously submitted a declaration pursuant to 37 C.F.R. § 1.132 by Dr. David B. Weiner with the response filed March 23, 2009 (copy appended hereto in Exhibits Appendix). The declaration lists the amino acid sequences from various leaders sequences and are labeled as IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1. These leader sequences have been identified by Dr. Weiner and show that not all leader sequences are the same. The declaration also shows the sequence similarity between the different leader sequences. The IgE leader sequence is not 100% identical to the other leader sequences. The declaration states, "[t]he alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes." (Weiner Declaration, ¶ 3). Therefore, the Office has failed to demonstrate that the "Ig leader" of the Walls reference is an "IgE leader" sequence. Therefore, the Office has failed to present a proper *prima facie* obviousness rejection because even if all the references were combined the combination does not yield the present invention. Thus, the claims are not obvious.

The Office has rejected the Declaration because of the apparent lack of Genbank or other source identifiers. The Office's request for Genbank accession numbers is improper. The Office

[5] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1320 (Fed. Cir. 2004).

[6] MPEP §2143.

cannot summarily dismiss the declaration without a reasonable basis to support its conclusion (See, *In Re Alton*, 76 F. 3d 1168, 1174-75 Fed. Cir. 1996). There is no requirement that the facts presented in the declaration be from a public database such as Genbank. The Declaration must be treated as a fact and when treated as such Applicants have provided sufficient evidence showing that not all leader sequences are the same. The Office has not provided any evidence to show that the facts presented in the declaration are incorrect. Rather than consider the evidence presented by Applicants in the declaration the Office has done what is prohibited. *Id.* When the evidence is properly considered the sequences demonstrate that not all leader sequences are the same. Therefore, the combination of the references fails to yield a composition comprising an IgE leader sequence as is presently claimed.

Accordingly claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 8, 32-37, 50, and 58-73 be withdrawn.

G. Claims 50 and 58-65 are Not Obvious in view of Klysner et al. (WO 02/20038) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31)

Claims 50 and 58-65 are also not obvious because the Klysner and Wang references each teach away from inserting a proteolytic cleavage sequence. The Wang and Klysner references teaches away for the reasons stated above and are hereby incorporated by reference.

Klysner also teaches away from the presently claimed invention because Klysner teaches that the epitopes should be simultaneously presented to the antigen presenting cells. (Klysner, entire document and, p. 13, lines 14-20). The inclusion of a proteolytic cleavage sequence that allows the epitopes to be separated would function to eliminate the likelihood of simultaneous presentation of the epitopes by the antigen presenting cells. "'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'" *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990

(Fed. Cir. 2006)). One of skill in the art would not have been led to insert a proteolytic cleavage sequence because it would be contrary to what the Klysner reference states is necessary for an effective use. Klysner teaches the simultaneous presentation of the epitopes by the antigen presenting cells. That is one of skill in the art would be discouraged from following the path of including a proteolytic cleavage sequence because both Klysner and Wang teach that keeping the epitopes together is important for the desired outcome. Thus, both the Klysner and Wang references teaches away from using a proteolytic cleavage sequence. The Office's use of Rutter to include a proteolytic cleavage sequence is improper because it contradicts the teachings of Klysner and Wang.

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Klysner and Wang references teach away from allowing the components to be separated and, therefore, a cleavage sequence based upon Rutter would not have been included.

In view of the foregoing, claims 50 and 58-65 are not obvious because the combination of the cited references fails to yield the presently claimed invention and the references teach away.

H. Claims 8, 32-37, 50, and 58-73 are Not Obvious in view of Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the references fails to teach all the elements of the claim. Claim 8 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent. Claim 50 is directed to a nucleic acid molecule comprising, in part, an IgE leader sequence. Claim 66 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE. Claim 72 is directed to a method of producing a protein comprising an IgE leader sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell and isolating said protein expressed thereby.

The Office has failed to put forward a proper *prima facie* obviousness rejection because even when all the references are combined the combination fails to yield the presently claimed invention. Specifically, the Office has failed to show that the combination yields a nucleic acid sequence with an IgE leader sequence or a nucleic acid sequence that encodes a protein comprising an IgE leader sequence. To determine obviousness, a four part test, as set forth in Graham v. John Deere Co., is employed to examine the: (i) content and scope of the prior art; (ii) level of ordinary skill in the art; (iii) differences between the prior art and the claimed invention; and (iv) objective evidence of non-obviousness.[7] To establish a *prima facie* case of obviousness, there must be some reason to combine the references, there must be some reasonable expectation of success based upon the teachings of the references and the prior art references, when combined, must teach or suggest all of the claim limitations.[8]

The Office alleges that the combination of references discloses each and every element of claims 8, 32-37, 50, 58-73. In support of this contention the Office states:

> Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain . . . and thus an "IgE leader" is the ***same sequence*** as an IgM, IgD, IgG, and IgA leader sequence…Thus, the "Ig leader" of Walls *et al.* is an "IgE leader."

(Final Office Action dated January 23, 2009, pages 9-10, emphasis added). Applicants have previously submitted a declaration pursuant to 37 C.F.R. § 1.132 by Dr. David B. Weiner with the response filed March 23, 2009 (copy appended hereto in Exhibits Appendix). The declaration lists the amino acid sequences from various leaders sequences and are labeled as IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1. These leader sequences have been identified by Dr. Weiner and show that not all leader sequences are the same. The declaration also shows the sequence similarity between the different leader sequences. The IgE leader sequence is not 100% identical to the

[7] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1320 (Fed. Cir. 2004).

[8] MPEP §2143.

other leader sequences. The declaration states, "[t]he alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes." (Weiner Declaration, ¶ 3). Therefore, the Office has failed to demonstrate that the "Ig leader" of the Walls reference is an "IgE leader." Therefore, the Office has failed to present a proper *prima facie* obviousness rejection because even if all the references were combined the combination does not yield the present invention. Thus, the claims are not obvious.

The Office has rejected the Declaration because of the apparent lack of Genbank or other source identifiers. The Office's request for Genbank accession numbers is improper. The Office cannot summarily dismiss the declaration without a reasonable basis to support its conclusion (See, *In Re Alton*, 76 F. 3d 1168, 1174-75 Fed. Cir. 1996). There is no requirement that the facts presented in the declaration be from a public database such as Genbank. The Declaration must be treated as a fact and when treated as such Applicants have provided evidence showing that not all leader sequences are the same. The Office has not provided any evidence to show that the facts presented in the declaration are incorrect. Rather than consider the evidence presented by Applicants in the declaration the Office has done what is prohibited. *Id.* When the evidence is properly considered the sequences demonstrate that not all leader sequences are the same. Therefore, the combination of the references fails to yield a composition comprising an IgE leader sequence as is presently claimed.

Accordingly, claims 8, 32-37, 50, and 58-73 are not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 8, 32-37, 50, and 58-73 be withdrawn.

I. Claims 50 and 58-65 are Not Obvious in view of Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326), and further in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 50 and 58-65 are also not obvious because the combination of the references teaches away from the presently claimed invention. Claims 50 and 58-65 recite in one form or another that the epitope of membrane IgE and the non-IgE helper T cell epitope are fused by a proteolytic cleavage sequence. As discussed above, Klysner and Wang teach away from an epitope of membrane IgE and a non-IgE helper T cell epitope being fused by a proteolytic

cleavage sequence. A "reference teaches away if it leaves the impression that the product would not have the property sought by the applicant." In re Gurley, 27 F. 3d 551, 553 (Fed. Cir. 1994, citing In re Caldwell, 319 F.2d 254, 256 (C.C.P.A. 1963)). Here, the Klysner and Wang references teach that the product should not contain a proteolytic cleavage sequence.

Not only do Klysner and Wang fail to teach or suggest a proteolytic cleavage sequence, but Klysner and Wang teach away from using a proteolytic cleavage sequence. The Office acknowledges that the Klysner and Wang references fail to disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes. (Final Office Action, page 6). The Office alleges that the Rutter reference cures this deficiency. The Rutter reference cannot cure this deficiency, however, because Klysner and Wang teach away from including a proteolytic cleavage sequence.

The claims are not obvious because the Klysner and Wang references each teach away from inserting a proteolytic cleavage sequence. The Wang reference teaches away for the reasons stated above and are hereby incorporated by reference. Klysner also teaches away because Klysner teaches that the epitopes should be simultaneously presented by the antigen presenting cells. (Klysner, p. 13, lines 14-20). The inclusion of a proteolytic cleavage sequence that allows the epitopes to be separated would function to eliminate the likelihood of simultaneous presentation of the epitopes by the antigen presenting cells. "'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'" Optivus Tech., Inc. v. Ion Beam Applications S.A., 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting In re Kahn, 441 F.3d 977, 990 (Fed. Cir. 2006)). One of skill in the art would not have been led to insert a proteolytic cleavage sequence because it would be contrary to what the Klysner reference states is necessary for its effective and intended purpose, that is the simultaneous presentation of the epitopes by the antigen presenting cells. Therefore, one of skill in the art would be discouraged from following the path of including a proteolytic cleavage sequence because both Klysner and Wang teach that keeping the epitopes together is important for the desired outcome. Thus, the Klysner reference teaches away from using a proteolytic cleavage sequence.

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Klysner and Wang references teach away from allowing the components to be

separated and, therefore, a cleavage sequence based upon Rutter would not have been included.

Accordingly, claims 50 and 58-65 are not obvious because the combination of the cited references fails to yield the presently claimed invention, as discussed herein, and the references teach away from the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 50 and 58-65 be withdrawn.

J. Claims 8, 32-37, 50, and 66-73 are Not Obvious in view of Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 66-73 are not obvious because the combination of the references fails to teach all the elements of the claim. Claim 8 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent. Claim 50 is directed to a nucleic acid molecule comprising, in part, an IgE leader sequence. Claim 66 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE. Claim 72 is directed to a method of producing a protein comprising an IgE leader sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell and isolating said protein expressed thereby.

The Office has failed to put forward a proper *prima facie* obviousness rejection because even when all the references are combined the combination fails to yield the presently claimed invention. Specifically, the Office has failed to show that the combination yields a nucleic acid sequence with an IgE leader sequence or a nucleic acid sequence that encodes a protein comprising an IgE leader sequence. To determine obviousness, a four part test, as set forth in Graham v. John Deere Co., is employed to examine the: (i) content and scope of the prior art; (ii) level of ordinary skill in the art; (iii) differences between the prior art and the claimed invention; and (iv) objective evidence of non-obviousness.[9] To establish a *prima facie* case of

[9] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 (continued...)

obviousness, there must be some reason to combine the references, there must be some reasonable expectation of success based upon the teachings of the references and the prior art references, when combined, must teach or suggest all of the claim limitations.[10]

The Office alleges that the combination of references discloses each and every element of claims 8, 32-37, 50, 66-73. In support of this contention the Office states:

> Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain . . . and thus an "IgE leader" is the ***same sequence*** as an IgM, IgD, IgG, and IgA leader sequence…Thus, the "Ig leader" of Walls *et al.* is an "IgE leader."

(Final Office Action dated January 23, 2009, pages 9-10, emphasis added). Applicants have previously submitted a declaration pursuant to 37 C.F.R. § 1.132 by Dr. David B. Weiner with the response filed March 23, 2009 (copy appended hereto in Exhibits Appendix). The declaration lists the amino acid sequences from various leaders sequences and are labeled as IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1. These leader sequences have been identified by Dr. Weiner and show that not all leader sequences are the same. The declaration also shows the sequence similarity between the different leader sequences. The IgE leader sequence is not 100% identical to the other leader sequences. The declaration states, "[t]he alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes." (Weiner Declaration, ¶ 3). Therefore, the Office has failed to demonstrate that the "Ig leader" of the Walls reference is an "IgE leader." Therefore, the Office has failed to present a proper *prima facie* obviousness rejection because even if all the references were combined the combination does not yield the present invention. Thus, the claims are not obvious.

The Office has rejected the Declaration because of the apparent lack of Genbank or other

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(continued...)

F.3d 1317, 1320 (Fed. Cir. 2004).

[10] MPEP §2143.

source identifiers. The Office's request for Genbank accession numbers is improper. The Office cannot summarily dismiss the declaration without a reasonable basis to support its conclusion (See, *In Re Alton*, 76 F. 3d 1168, 1174-75 Fed. Cir. 1996). There is no requirement that the facts presented in the declaration be from a public database such as Genbank. The Declaration must be treated as a fact and when treated as such Applicants have provided evidence showing that not all leader sequences are the same. The Office has not provided any evidence to show that the facts presented in the declaration are incorrect. Rather than consider the evidence presented by Applicants in the declaration the Office has done what is prohibited. *Id.* When the evidence is properly considered the sequences demonstrate that not all leader sequences are the same. Therefore, the combination of the references fails to yield a composition comprising an IgE leader sequence as is presently claimed.

Accordingly, claims 8, 32-37, 50, and 66-73 are not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 8, 32-37, 50, and 66-73 be withdrawn.

K. Claim 50 is Not Obvious in view of Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Applicants also note that Claim 50 is not obvious because the combination of the references fails to yield claim 50. Claim 50 depends upon claim 1. Claim 1 recites that the nucleic acid molecule comprises an epitope of membrane IgE and an nonIgE helper T cell epitope that are fused by a proteolytic cleavage sequence. The combination of the references does not teach or suggest a proteolytic cleavage sequence. As admitted by the Office the Klysner reference fails to teach a proteolytic cleavage sequence. Neither Walls nor Janeway cure this deficiency. In fact, the Office's rejection under this set of references fails to discuss the proteolytic cleavage sequence of claim 50. Accordingly, the combination fails to yield claim 50 for the foregoing reasons. Therefore, claim 50 is not obvious in view of Klysner (WO 02/20038) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al.

Accordingly, claim 50 is not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully

request that the rejection of claim 50 be withdrawn.

L. Claims 8, 32-37, 50, and 66-73 are Not Obvious in view of Klysner (WO 02/20038) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Claims 8, 32-37, 50, and 66-73 are not obvious because the combination of the references fails to teach all the elements of the claim. Claim 8 is directed to a vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent. Claim 50 is directed to a nucleic acid molecule comprising, in part, an IgE leader sequence. Claim 66 is directed to a host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE. Claim 72 is directed to a method of producing a protein comprising an IgE leader sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell and isolating said protein expressed thereby.

The Office has failed to put forward a proper *prima facie* obviousness rejection because even when all the references are combined the combination fails to yield the presently claimed invention. Specifically, the Office has failed to show that the combination yields a nucleic acid sequence with an IgE leader sequence or a nucleic acid sequence that encodes a protein comprising an IgE leader sequence. To determine obviousness, a four part test, as set forth in Graham v. John Deere Co., is employed to examine the: (i) content and scope of the prior art; (ii) level of ordinary skill in the art; (iii) differences between the prior art and the claimed invention; and (iv) objective evidence of non-obviousness.[11] To establish a *prima facie* case of obviousness, there must be some reason to combine the references, there must be some

[11] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1320 (Fed. Cir. 2004).

reasonable expectation of success based upon the teachings of the references and the prior art references, when combined, must teach or suggest all of the claim limitations.[12]

The Office alleges that the combination of references discloses each and every element of claims 8, 32-37, 50, 66-73. In support of this contention the Office states:

> Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain . . . and thus an "IgE leader" is the ***same sequence*** as an IgM, IgD, IgG, and IgA leader sequence…Thus, the "Ig leader" of Walls *et al.* is an "IgE leader."

(Final Office Action dated January 23, 2009, pages 9-10, emphasis added). Applicants have previously submitted a declaration pursuant to 37 C.F.R. § 1.132 by Dr. David B. Weiner with the response filed March 23, 2009 (copy appended hereto in Exhibits Appendix). The declaration lists the amino acid sequences from various leaders sequences and are labeled as IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1. These leader sequences have been identified by Dr. Weiner and show that not all leader sequences are the same. The declaration also shows the sequence similarity between the different leader sequences. The IgE leader sequence is not 100% identical to the other leader sequences. The declaration states, "[t]he alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes." (Weiner Declaration, ¶ 3). Therefore, the Office has failed to demonstrate that the "Ig leader" of the Walls reference is an "IgE leader." Therefore, the Office has failed to present a proper *prima facie* obviousness rejection because even if all the references were combined the combination does not yield the present invention. Thus, the claims are not obvious.

The Office has rejected the Declaration because of the apparent lack of Genbank or other source identifiers. The Office's request for Genbank accession numbers is improper. The Office cannot summarily dismiss the declaration without a reasonable basis to support its conclusion (See, *In Re Alton*, 76 F. 3d 1168, 1174-75 Fed. Cir. 1996). There is no requirement that the facts presented in the declaration be from a public database such as Genbank. The Declaration must

[12] MPEP §2143.

be treated as a fact and when treated as such Applicants have provided evidence showing that not all leader sequences are the same. The Office has not provided any evidence to show that the facts presented in the declaration are incorrect. Rather than consider the evidence presented by Applicants in the declaration the Office has done what is prohibited. *Id.* When the evidence is properly considered the sequences demonstrate that not all leader sequences are the same. Therefore, the combination of the references fails to yield a composition comprising an IgE leader sequence as is presently claimed.

Accordingly, claims 8, 32-37, 50, and 66-73 are not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claims 8, 32-37, 50, and 58-73 be withdrawn.

M. Claim 50 are Not Obvious in view of Klysner (WO 02/20038) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al. (Immunobiolgy, 3rd edition, Garland Publications, 1997, pages 3:26-3:31)

Applicants also note that Claim 50 is not obvious because the combination of the references fails to yield claim 50. Claim 50 depends upon claim 1. Claim 1 recites that the nucleic acid molecule comprises an epitope of membrane IgE and an nonIgE helper T cell epitope that are fused by a proteolytic cleavage sequence. The combination of the references does not teach or suggest a proteolytic cleavage sequence. As admitted by the Office the Klysner reference fails to teach a proteolytic cleavage sequence. Neither Walls nor Janeway cure this deficiency. In fact, the Office's rejection under this set of references fails to discuss the proteolytic cleavage sequence of claim 50. Accordingly, the combination fails to yield claim 50 for the foregoing reasons. Therefore, claim 50 is not obvious in view of Klysner (WO 02/20038) in view of Walls et al. (Nucleic Acids Research, 1993, 21 :2921-2929) as evidenced by Janeway et al.

Accordingly claim 50 is not obvious because the combination of the cited references fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection of claim 50 be withdrawn.

CONCLUSION

In light of the arguments and points discussed more fully above, the rejections presented in the January 23, 2009 Office Action should be withdrawn as such rejections are based upon references that either teach away from the presently claimed invention or do not yield the presently claimed invention when combined. As a result, the pending claims are allowable, and Appellant respectfully requests that the Board so rule.

Appellant has filed herewith the appropriate payment of fees as required. The Commissioner for Patents is hereby authorized to charge any additional fees, or any difference in fees, which may be required to Deposit Account No. 50-0436. Please refund any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,
PEPPER HAMILTON LLP

/Daniel M. Scolnick, Reg. No. 52201/
Daniel M. Scolnick, Ph.D.
Registration No. 52,201

Dated: **March 1, 2010**

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VIII. CLAIMS APPENDIX

1. **(Previously presented)** An isolated nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one nonIgE helper T cell epitope, and being free of epitopes of serum IgE, wherein said epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence.

2. **(Previously presented)** The nucleic acid molecule of claim 1 wherein said protein comprises membrane IgE or fragment thereof.

3. **(Previously presented)** The nucleic acid molecule of claim 2 wherein said protein comprises membrane IgE.

4. **(Canceled)**

5. **(Previously presented)** The nucleic acid molecule of claim 1 wherein the coding sequence encoding the at least one non-IgE helper T cell epitope encodes tetanus toxoid Th epitope.

6. **(Previously presented)** The nucleic acid molecule of claim 1 wherein said nucleic acid molecule is a plasmid.

7. **(Previously presented)** The nucleic acid molecule of claim 1 wherein said nucleic acid molecule is incorporated in a viral vector or a bacterial cell.

8. **(Previously presented)** A vaccine composition comprising a nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent.

9-21 **(Canceled)**

22. **(Previously presented)** A host cell comprising an isolated nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one nonIgE helper T cell epitope, and being free of epitopes of serum IgE, wherein said epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence.

23 **(Previously presented)** The host cell of claim 22 wherein said protein comprises membrane IgE or fragment thereof.

24 **(Previously presented)** The host cell of claim 22 wherein said protein comprises membrane IgE.

25. **(Canceled)**

26. **(Previously presented)** The host cell of claim 22 wherein the coding sequence encoding the at least one non-IgE helper T cell epitope encodes tetanus toxoid Th epitope.

27. **(Previously presented)** The host cell of claim 22 wherein said nucleic acid molecule is a plasmid.

28 **(Previously presented)** A method of producing a protein comprising at least one membrane IgE and at least one non-IGE helper T cell epitope and being free of epitopes of serum IgE, wherein said epitope of membrane IgE and said nonIgE helper T cell epitope are fused by a proteolytic cleavage sequence

comprising culturing a host cell of claim 22 and isolating said protein expressed thereby.

29. **(Previously presented)** The method of claim 28, wherein the protein is isolated using an antibody that specifically binds to said protein.

30-31. **(Canceled)**

32. **(Previously presented)** The vaccine of claim 8 wherein said protein comprises membrane IgE or fragment thereof.

33. **(Previously presented)** The vaccine of claim 8 wherein said protein comprises membrane IgE.

34. **(Previously presented)** The vaccine of claim 8 further comprising coding sequence encoding at least one non-IgE helper T cell epitope.

35. **(Previously presented)** The vaccine of claim 34 wherein the coding sequence encoding the at least one non-IgE helper T cell epitope encodes tetanus toxoid Th epitope.

36. **(Previously presented)** The vaccine of claim 8 wherein said nucleic acid molecule is a plasmid.

37. **(Previously presented)** The vaccine of claim 8 wherein said nucleic acid molecule is incorporated in a viral vector or a bacterial cell.

38-49. **(Canceled)**

50. **(Previously presented)** The isolated nucleic acid molecule of claim 1, further comprising coding sequence encoding an IgE leader sequence.

51. **(Previously presented)** An isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE and being free of epitopes of serum IgE.

52. **(Previously presented)** The isolated nucleic acid molecule of claim 51, further comprising coding sequence encoding at least one nonIgE helper T cell epitope.

53. **(Previously presented)** The isolated nucleic acid molecule of claim 51, wherein said protein comprises membrane IgE or fragment thereof.

54. **(Previously presented w)** The nucleic acid molecule of claim 54, wherein said protein comprises membrane IgE.

55. **(Previously presented)** The nucleic acid molecule of claim 52, wherein the coding sequence encoding the at least one nonIgE helper T cell epitope encodes tetanus toxoid Th epitope.

56. **(Previously presented)** The nucleic acid molecule of claim 51, wherein said nucleic acid molecule is a plasmid.

57. **(Previously presented)** The nucleic acid molecule of claim 51, wherein said nucleic acid molecule is incorporated in a viral vector a bacterial cell.

58. **(Previously presented)** The vaccine composition of claim 34, wherein said at least one epitope of membrane IgE and said at least one non-IgE helper T cell epitope are fused by a proteolytic cleavage sequence.

59. **(Previously presented)** A vaccine composition comprising a nucleic acid molecule that encodes a protein comprising at least one epitope of membrane IgE and at least one non-IgE helper T cell epitope, being free of epitopes of serum IgE, and a pharmaceutically acceptable carrier or diluent, wherein said at least one epitope of membrane IgE and said at least one non-IgE helper T cell epitope are fused by a proteolytic cleavage sequence.

60. **(Previously presented)** The vaccine composition of claim 59, wherein said protein

comprises membrane IgE or fragment thereof.

61. **(Previously presented)** The vaccine composition of claim 59, wherein said protein comprises membrane IgE.

62. **(Previously presented)** The vaccine composition of claim 59, wherein the coding sequence encoding the at least one non-IgE helper T cell epitope encodes tetanus toxoid Th epitope.

63. **(Previously presented)** The vaccine composition of claim 59, wherein said nucleic acid molecule is a plasmid.

64. **(Previously presented)** The vaccine composition of claim 59, wherein said nucleic acid molecule is incorporated in a viral vector or a bacterial cell.

65. **(Previously presented)** The host cell of claim 22, wherein said nucleic acid molecule further comprises a coding sequence encoding an IgE leader sequence.

66. **(Previously presented)** A host cell comprising an isolated nucleic acid molecule that encodes a protein comprising an IgE leader sequence and at least one epitope of membrane IgE, and being free of epitopes of serum IgE.

67. **(Previously presented)** The host cell of claim 66, wherein said nucleic acid molecule further comprising coding sequence that encodes a protein comprising at least one nonIgE helper T cell epitope.

68. **(Previously presented)** The host cell of claim 66, wherein said protein comprises membrane IgE or fragment thereof.

69. **(Previously presented)** The host cell of claim 66, wherein said protein comprises membrane IgE.

70. **(Previously presented)** The host cell of claim 67, wherein the coding sequence encoding the at least one non-IgE helper T cell epitope encodes tetanus toxoid Th epitope.

71. **(Previously presented)** The host cell of claim 66, wherein said nucleic acid molecule is a plasmid.

72. **(Previously presented)** A method of producing a protein comprising an IgE leader

sequence and at least one membrane IgE epitope and being free of epitopes of serum IgE comprising culturing a host cell of claim 66 and isolating said protein expressed thereby.

73. **(Previously presented)** The method of claim 72, wherein the protein is isolated using an antibody that specifically binds to said protein.

IX. EVIDENCE APPENDIX

Declaration of David B. Weiner entered into the record by the Examiner on April 7, 2009 and is enclosed herewith.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: **Arnold I. Levinson *et al.***

Serial No.:	**10/518,701**	Group Art Unit:	1644
Filing Date:	**September 1, 2005**	Examiner:	M. E. Szperka
		Confirmation No.:	5645

For: **VACCINES FOR SUPPRESSING IgE-MEDIATED ALLERGIC DISEASE AND METHODS FOR USING THE SAME**

Commissioner for Patents
P.O.Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION OF DR. DAVID B. WEINER

I, David B. Weiner, do hereby declare as follows:

1. I am a co-inventor of the subject matter claimed in the above-identified U.S. Patent Application.

2. I am a Professor at the University of Pennsylvania School of Medicine and I have an appointment in the Department of Pathology & Laboratory Medicine.

3. The following is a list of Ig leader sequences from IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1.:

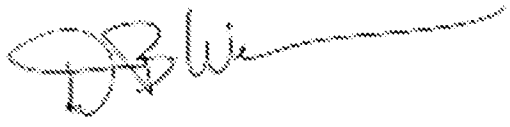
IgE variable (IgELS)	M D W T W – I L F L V A A A T **R V** H S
IgA constant	M D W T W **S** I L F L V A A A T **G V** H S
IgA variable1	M D W T W **S** I L F L V A A A T **G A** H S
IgA variable2	M D W T W **R** I L F L V A A A T **S A** H S
IgA variable3	M D W T W **R** I L F L V A A A T **G A** H S
IgG constant	M D W T W **R** I L F L V A A A T **S A** H S
IgM variable	M D W T W **R** I L F L V A A A T **S A** H S
IgM VH1	M D W T W **R** I L F L V A A A T **G A** H S

The following table presents the percent similarity between the IgE leader sequence and the other listed leader sequences.

	IgA constant	IgA variable1	IgA variable2	IgA variable3	IgG constant	IgM variable	IgM VH1
IgELS	94.4%	88.9%	88.9%	88.9%	88.9%	88.9%	88.9%

The alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes.

4. I declare that all statements made herein are of our own knowledge true and statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



MARCH 20, 2009

David B. Weiner, Ph.D. Date

X. RELATED PROCEEDINGS APPENDIX

None.